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Theoretical Study of Mechanism and Selectivity of Copper-Catalyzed C–H Bond Amidation of Indoles

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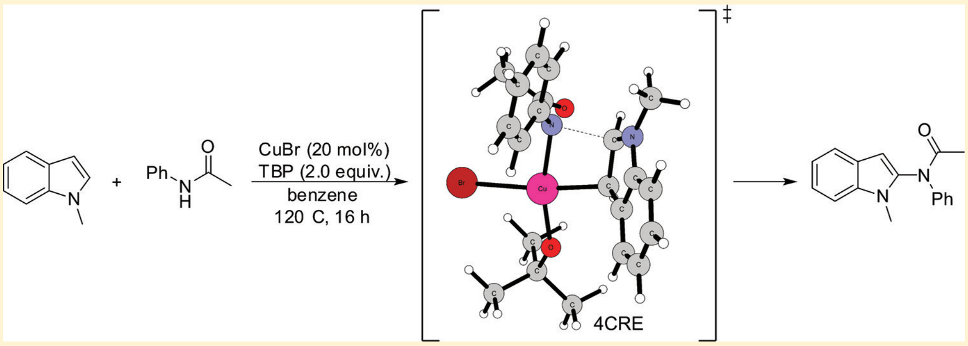
Ⓢ *Supporting Information*

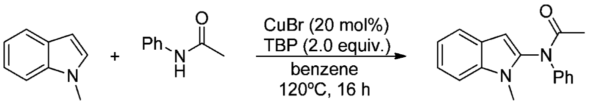


ABSTRACT: Density functional theory calculations are used to study the reaction mechanism and origins of C2 selectivity in a copper(I)-catalyzed amidation of indoles. It is shown that concerted metalation–deprotonation is not able to reproduce the observed regioselectivity. Instead, an unprecedented mechanism based on a four-center reductive elimination is proposed to be responsible for the reaction outcome. This mechanism has a lower reaction barrier and is able to reproduce the experimentally observed selectivity. A possible alternative mechanism involving a Cu(II) species instead of Cu(III) is presented, but it is shown that higher energy barriers are associated with this mechanism. An important technical detail is that addition of dispersion effects to the B3LYP results is necessary to reproduce the observed selectivity, although not important for the overall mechanistic proposal.

1. INTRODUCTION

Aromatic compound functionalizations are reactions of fundamental importance in organic chemistry,[1] and although many methodologies to effect different modifications of these substrates are known, extraordinary efforts are still devoted to the discovery and development of new reactions.[2] Particularly interesting are methods that allow for direct functionalization of aromatic C–H bonds, thus avoiding troublesome and waste-producing transformations.[3,4] The main drawbacks of these strategies reside in the problematic control of the selectivity, arising from the ubiquitous presence of C–H bonds in organic molecules. The most common way to induce selectivity in aromatic C–H bond functionalizations relies on the presence of chelating functional groups on the aromatic substrate that direct the metalation to a specific position.[5] A less exploited but very promising strategy to effect position-selective C–H activation involves the use of ligands able to direct the functionalization.[6]

Recently, an interesting copper-catalyzed regioselective oxidative amidation of 1-methylindoles was reported by Li and co-workers (eq 1).[7] The reaction was performed with a catalytic amount of copper(I) bromide using *tert*-butyl peroxide (TBP) as the overstoichiometric oxidant in benzene at 120 °C, and only the formation of the C2-amidated product was observed. Different amides ranging from electron-rich to electron-poor could be used, with yields up to 70%.



(1)

1 2 3

60% yield

The reaction mechanism shown in Scheme 1 was proposed by the authors.[7] In this mechanism, the initial oxidation of the Cu(I) salt (**A**) to give a Cu(III) species (**B**) is followed by deprotonation of the amide to form the reactive intermediate **C**. This then reacts regioselectively with the substrate to form a C2-metalated indole (**D**), which, after reductive elimination, affords the product and regenerates the Cu(I) species **A**. However, no explanation for the observed regioselectivity was put forward.

Considering the high relevance of regioselective C–H functionalization of aromatic compounds and the current lack of a detailed understanding of the mechanism and the selectivity, we decided to use density functional theory (DFT) to investigate

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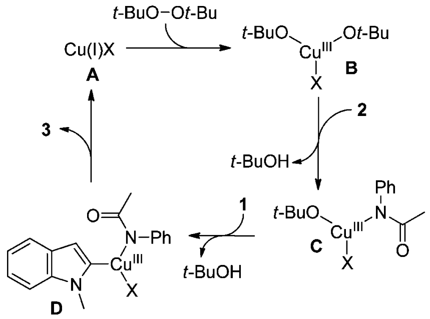
Scheme 1. Reaction Mechanism Proposed Originally for the C2 Amidation of *N*-Methylindole[7]



both the reaction mechanism and the origins of the observed selectivity of this reaction. The calculations show that the proposed mechanism is not able to reproduce the experimentally observed C2 selectivity. Instead, an unprecedented mechanism in which copper coordinates the indole and the amide nitrogen attacks the adjacent position of the ring in a four-center reductive elimination transition state is shown to account for the observed regioselectivity. In addition, the plausibility of the reaction being catalyzed by Cu(II) is also considered in this study on the basis of both the thermodynamics of formation of the Cu(II) species and the barriers for the amidation step.

2. COMPUTATIONAL METHODS

All calculations reported in the present study were carried out using density functional theory with the B3LYP functional,[8] as implemented in the Gaussian03 program package.[9] For geometry optimizations, the 6-31G(*d*,*p*) basis set was used for the C, N, O, and H elements and the LANL2DZ[10] pseudopotential for Cu and Br. On the basis of these optimized geometries, single-point calculations were carried out with the 6-311+G(2*d*,2*p*) basis set for all elements. The stationary points were confirmed as minima (no imaginary frequencies) or transition states (only one imaginary frequency) by analytical frequency calculations at the same theory level as the geometry optimizations. Selected reaction pathways were subjected to intrinsic reaction coordinate (IRC)[11] analysis in order to trace their paths and to confirm that the optimized transition state (TS) structures connect the correct reactants and products. The reported energies are Gibbs free energies that include zero-point vibrational corrections, thermal corrections at 298 K, and solvation free energies. The latter are calculated as single-point corrections on the optimized structures using the conductor-like polarizable continuum model (CPCM)[12] method with the UAKS radii and with the parameters for benzene. Unless stated otherwise, all energies are also corrected for dispersion effects using the B3LYP-D method of Grimme.[13] Recent reports have shown that inclusion of dispersion effects can significantly improve the performance of the B3LYP method.[14] For the Cu(I)/Cu(III) mechanism, both the singlet and the triplet spin states were considered. All stationary points were found to be on the singlet surface, except **B**, **B′**, and **B″** (see below), for which the triplet state was found to be 3−8 kcal/mol lower than the singlet. For the Cu(I)/Cu(II) mechanism, all stationary points were located on the doublet surface.

3. RESULTS AND DISCUSSION

In this section we first discuss the calculations concerning the originally proposed mechanism and show that, although the reaction barriers are energetically plausible, the selectivity is not reproduced. We then present a new mechanism that has lower barriers and that can account for the selectivity. Finally, we discuss the possibility of the reaction being catalyzed by Cu(II) instead of Cu(III).

3.1. Cu(I)/Cu(III) Mechanisms.

The originally proposed mechanism is a Cu(I)/Cu(III) catalytic cycle based on a metalation/deprotonation step followed by reductive elimination (Scheme 1). We start the discussion from the $Cu^I(Br)(TBP)$ complex.[15] From there, the barrier for the oxidation to afford the Cu(III) intermediate **B** (X = Br) is calculated to be 16.9 kcal/mol, with the step being exothermic by 4.0 kcal/mol. Optimized structures of the stationary points are shown alongside the calculated energy profile in Figure 1. Next, the amide binds to the Cu(III) center through the oxygen atom, resulting in structure **B′**, which is calculated to be 2.1 kcal/mol lower than **B**. From **B′**, the calculations show that a proton transfer between the amide and the *t*-BuO-ligand to yield **B″** intermediate is very facile, being endothermic by only 1.6 kcal/mol, which is also calculated to be the barrier for the transfer.[16] Next step, the exchange of the *t*-BuOH ligand for the

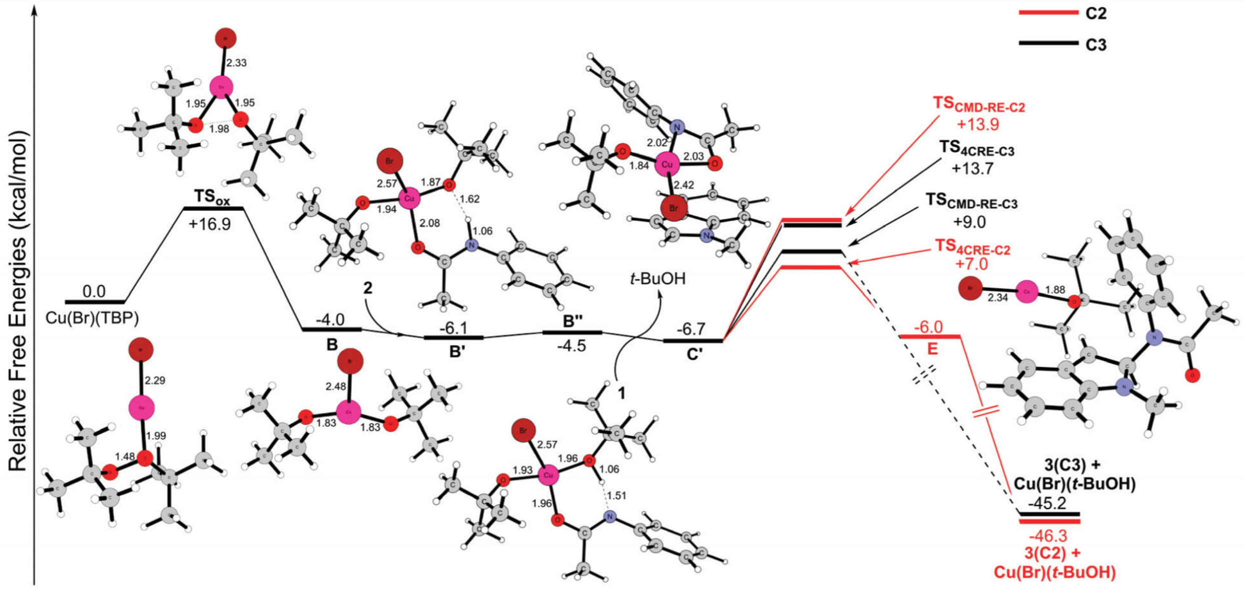
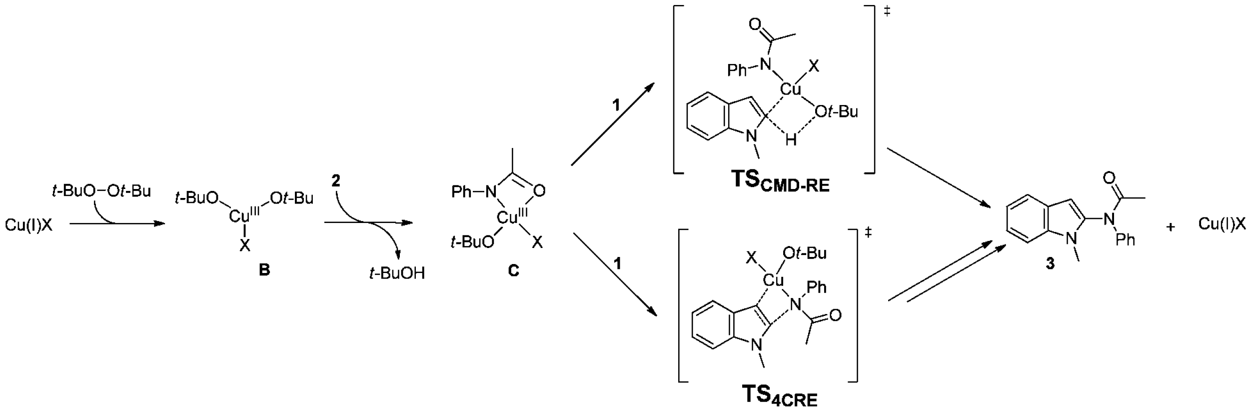


Figure 1. Free energy profile for the amidation through Cu(I)/Cu(III) mechanisms.

Scheme 2. Possible Reaction Mechanisms for C2 Amidation of *N*-Methylindole, According to the Current DFT Calculations



indole substrate **1** is calculated to be exothermic by 2.2 kcal/mol. It turns out that once the *t*-BuOH ligand is removed, the deprotonated amide in **C** binds bidentately to the copper, giving a square planar structure. Therefore, in the complex between **C** and **1** (called **C′**), it is seen that the indole substrate does not coordinate to the copper.

The results so far show thus that the formation of intermediate **C′** is energetically feasible. Next, the critical indole amidation reaction takes place. From **C′**, we have optimized the transition states for metalation/deprotonation on positions 2 and 3 of the *N*-methylindole. It turns out that for both positions the well-established concerted metalation−deprotonation (CMD)[17] occurs concertedly with reductive elimination to yield the final products (see Scheme 2). The optimized transition states, called $\mathbf{TS}_{\text{CMD-RE-C2}}$ and $\mathbf{TS}_{\text{CMD-RE-C3}}$, are shown in Figure 2. The energy barriers are calculated to be 20.6 and 15.7 kcal/mol for amidation on the C2 and C3 positions, respectively. Although these barriers are plausible, they clearly fail to reproduce the observed C2-selectivity. The reason for the preference of this mechanism for position 3 is the inherent higher nucleophilicity of this carbon compared to C2.

Searching for an alternative mechanism that can account for the C2 selectivity, we found that from **C′** a four-center reductive elimination (4CRE) can take place, with the metal coordinating to either C2 or C3 of the indole and the amide nitrogen attacking the adjacent position ($\mathbf{TS}_{\text{4CRE-C2}}$ and $\mathbf{TS}_{\text{4CRE-C3}}$; see Figure 1 for potential energy profile, Figure 2 for optimized transition state structures, and Scheme 2 for a schematic drawing). This mechanism is similar to the Heck-like mechanism reported recently by Wu and co-workers in a mechanistic study of a meta-selective anilide arylation.[18] However, it should be pointed out that in our case no intermediate could be found with the copper being bound to the aromatic ring, neither before nor after the key transition state.

The amidation on C2 is, in this case, preferred over C3 by 6.7 kcal/mol (13.7 vs 20.4 kcal/mol). These barriers should however be compared to the ones of the CMD-RE mechanism discussed above, which were 20.6 and 15.7 kcal/mol for amidation on the C2 and C3, respectively. It is important to note that when the reaction occurs on C2 with the 4CRE mechanism, the copper ion is interacting with C3, and vice versa. The preference for the reaction to occur on C2 could thus again be explained by the higher inherent nucleophilicity of C3 of indole, which makes the coordination of this center to the copper more preferred and hence the amide attack on C2 lower in energy. The lowest amidation barrier is thus seen for 4CRE on C2, which is 2.0 kcal/mol lower than the barrier for CMD-RE on C3. This value is in qualitative agreement with the experimental findings, which showed the exclusive formation of the C2-amidated product.

To complete the reaction, the proton of the amidated carbon in intermediate **E** needs to be removed. This proton is highly acidic and could easily be transferred to the *t*-BuO-ligand of the Cu(I) species. We could not locate the transition state for this deprotonation because the proton always spontaneously moved to the *t*-BuO-ligand in the geometry optimization. The final product is calculated to be 39.6 kcal/mol lower than **C′**.

Here, a very important technical point should be discussed. As mentioned in the Computational Methods above, addition of dispersion corrections to B3LYP has been shown to provide

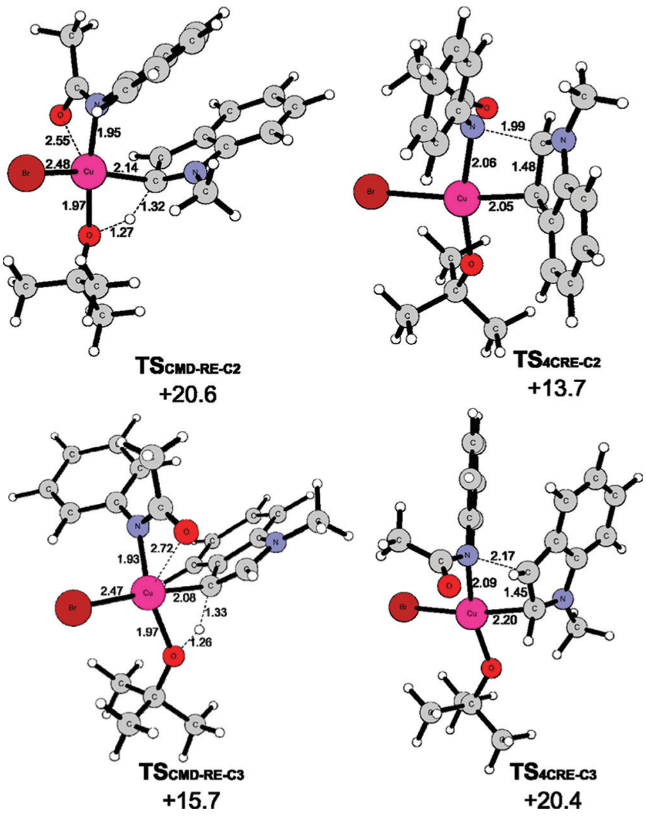


Figure 2. Optimized structures of transition states for Cu(I)/Cu(III) mechanisms. Distances are in Ångstroms. Free energies (relative to **C′**) are given in kcal/mol.

improved results in a number of applications in recent years.[14] In the case of the selectivity studied here, it turns out that this correction is crucial in order to reproduce the experimental trend. Without inclusion of the dispersion correction, B3LYP fails to reproduce the experimental selectivity, whereas B3LYP-D gives the correct ordering of the transition states (Table 1).

Table 1. Free Energies (kcal/mol) of the Critical Transition States Using Different Functionals[a]

	B3LYP	B3LYP-D	M06
$\mathbf{TS}_{\text{CMD-RE-C2}}$	+24.5	+20.6	+21.0
$\mathbf{TS}_{\text{CMD-RE-C3}}$	**+18.7**	+15.7	+15.9
$\mathbf{TS}_{\text{4CRE-C2}}$	+23.2	**+13.7**	**+14.2**
$\mathbf{TS}_{\text{4CRE-C3}}$	+28.3	+20.4	+22.6

[a] Barriers are calculated as single-points using the 6-311+G(2d,2p) basis set on the B3LYP-optimized geometries. The values are including solvation corrections and are relative to **C**′.

Furthermore, single-point energies calculated using the M06 functional,[19] which includes noncovalent interactions in its training set, are consistent with the B3LYP-D results (see Table 1). These findings further corroborate the importance of the dispersion correction to the well-established B3LYP functional.

To investigate the substituent effect on both the amide and the indole reactants, we have calculated the barriers of both the CMD-RE and 4CRE mechanisms on both C2 and C3 positions for a number of substituted substrates (see Table 2).

For the amide substrate, three substitutions were examined, namely, *p*-methoxy-, *m*-chloro-, and *p*-cyanophenyl amides. Experimentally, *p*-methoxy and *m*-chloro phenyl substituted amides showed similar reactivities as the unsubstituted amide **2**, affording the 2-amidated indole in moderate yield and complete C2 regioselectivity, whereas the *p*-cyanophenyl substituted amide was reported to be unreactive under the reaction conditions.

Our calculations show that all three substitutions yield only slightly higher barriers (less than 2 kcal/mol) compared to the unsubstituted case (Table 2), with the lowest barrier being for the reaction occurring on C2 position through a 4CRE mechanism. The calculations thus reproduce the *p*-methoxy and *m*-chloro substitutions but show that *p*-cyanophenyl should also behave in the same way, which is not the case experimentally. This fact indicates that perhaps something else is taking place for this specific substrate, like for example, oxidative decomposition of either the reactant or the product. It is very difficult to speculate with the limited experimental information available.

We have also studied the substitution effect on the indole substrate by considering two cases, namely, 1-methyl-4-cyanoindole and 1,2-dimethylindole. In both cases, no amidation product was observed experimentally.

In the case of 1-methyl-4-cyanoindole, we found significantly higher barriers for all the transition states, with the lowest being the one for a CMD-RE occurring on C3 (+21.9 kcal/mol). Apparently, the cyano group makes the indole less electron-rich to an extent that it disfavors the reaction according to both considered mechanisms, which is consistent with the experimental observations.

For the reaction of 1,2-dimethylindole, we calculated the barrier for the reaction to occur on C3 position through either a CMD-RE or a 4CRE mechanism. In this case, quite low barriers were found (12.7 and 14.1 kcal/mol, respectively), which indicates that the reaction should be possible to occur. This is of course inconsistent with the experiments, which showed that no C3-amidation product was obtained for this substrate. It is known that 2-alkyl indoles are prone to oxidation and eventually dimerization.[20] This is a likely scenario in the harsh reaction conditions required for the studied reaction, which can possibly explain why no product was observed.

3.2. Cu(I)/Cu(II) Mechanism.

A recent report on the mechanism of Cu-catalyzed C−H amination of alkanes demonstrated that a Cu(II) species is actually responsible for the catalysis.[21] Since the reaction conditions (Cu^{I} salt with TBP in benzene) are similar to those of the amidation reaction studied in the present paper, we decided to investigate whether a Cu(II) species can be involved also in this reaction.

First, we examined whether the formation of Cu(II) from the Cu(III) species is thermodynamically plausible. This constitutes the initial steps of the process, if we assume that the reaction between CuBr and TBP generates the Cu(III)-intermediate **B** (Scheme 3).[22]

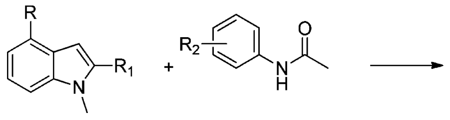
Indeed, the formation of a Cu(II) species was found to be energetically feasible. One possibility is the formation of CuBr_2 and Cu(*t*-BuO)$_2$ (**F**) from the reaction between **B** and CuBr (eq 2). This process was calculated to be exothermic by 14.8 kcal/mol. Alternatively, the formation of 2 equiv of Cu(*t*-BuO)Br from the same reactants (eq 3) is even more exothermic, now by 23.7 kcal/mol.

$$\text{Cu(I)Br} + \text{Cu(III)}(t\text{-BuO})_2\text{Br} \rightarrow \text{Cu(II)Br}_2 + \text{Cu(II)}(t\text{-BuO})_2 \tag{2}$$

$$\text{Cu(I)Br} + \text{Cu(III)}(t\text{-BuO})_2\text{Br} \rightarrow 2\text{Cu(II)}(t\text{-BuO})\text{Br} \tag{3}$$

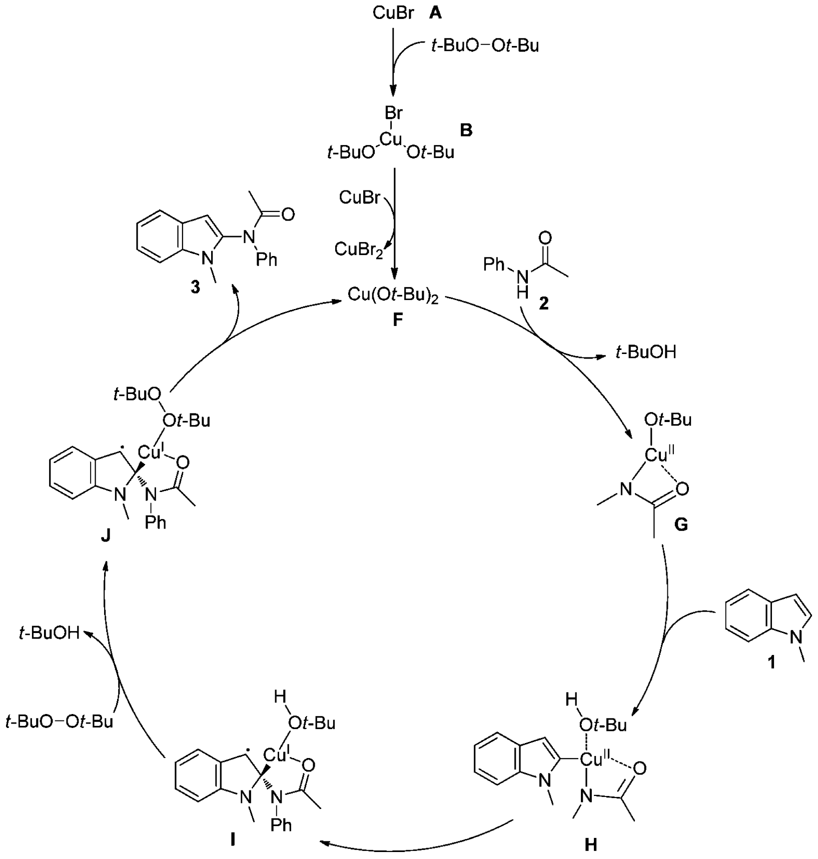
The reaction can then follow the mechanism of Scheme 3. Since the reoxidation of Cu(I) after the first catalytic cycle will regenerate the Cu(*t*-BuO)$_2$ species, we used this as a precatalyst for studying the Cu(I)/Cu(II) mechanism.

Table 2. Free Energies (kcal/mol) of the Critical Transition States for the Reactions of Substituted Substrates



	R = R$_1$ = R$_2$ = H	R = R$_1$ = H R$_2$ = *p*-MeO	R = R$_1$ = H R$_2$ = *m*-Cl	R = R$_1$ = H R$_2$ = *p*-CN	R = CN R$_1$ = R$_2$ = H	R = R$_2$ = H R$_1$ = Me
$\mathbf{TS}_{\text{CMD-RE-C2}}$	+20.6	+22.1	+21.3	+21.1	+26.3	
$\mathbf{TS}_{\text{CMD-RE-C3}}$	+15.7	+17.7	+17.1	+15.4	+21.9	+12.7
$\mathbf{TS}_{\text{4CRE-C2}}$	+13.7	+15.6	+14.6	+14.8	+22.7	
$\mathbf{TS}_{\text{4CRE-C3}}$	+20.4	+21.0	+20.7	+20.4	+26.2	+14.1

Scheme 3. Possible Mechanism for the Amidation on C2 through a Cu(I)/Cu(II) Reaction[a]



[a]The barriers were however found to be considerably higher than for the 4CRE mechanism; see text.

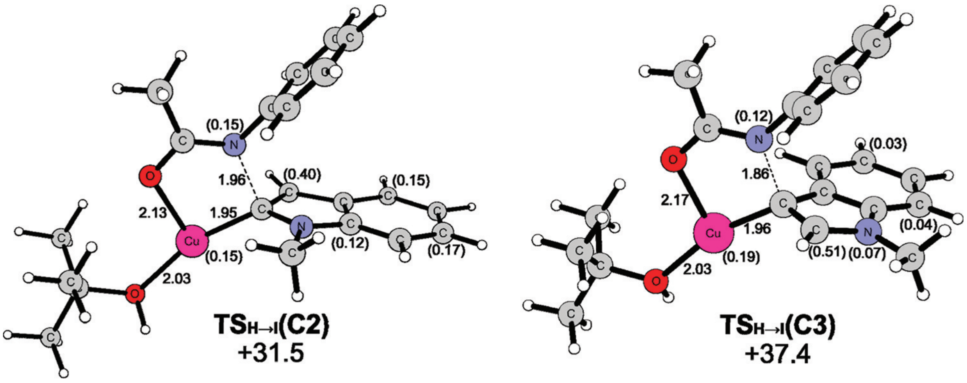


Figure 3. Optimized structures for the rate-determining TS leading to intermediate **I** in the Cu(II) mechanism. Distances in Ångstroms. Relevant spin densities are given in parentheses.

The deprotonation of amide **2** can be effected by Cu(*t*-BuO)$_2$ (**F**), very similarly to what was found for the Cu(III) mechanism (see **B′** → **B″** in Figure 1). We found that intermediate **G** can react with substrate **1** in a CMD either on C2 or C3 positions, leading to the formation of metalated-indole intermediate **H**. The subsequent C−N bond formation implies the reduction of Cu(II) to Cu(I) and the generation of a radical on the indole. This step is the rate-determining step for this mechanism for the reaction occurring either on C2 or C3 positions, with barriers being 31.5 and 37.4 kcal/mol, respectively (see optimized structures for $\mathbf{TS}_{\mathrm{H\to I}}$(**C2**) and $\mathbf{TS}_{\mathrm{H\to I}}$(**C3**) in Figure 3). The energy difference, favoring the reaction on C2 position, can be explained by the higher degree of stabilization of the radical in $\mathbf{TS}_{\mathrm{H\to I}}$(**C2**) and in the resulting intermediate **I**(**C2**), compared to $\mathbf{TS}_{\mathrm{H\to I}}$(**C3**) and **I**(**C3**). To complete the cycle, a reoxidation of Cu(I) to Cu(II) and oxidation/rearomatization of indole are necessary. This can be effected by a TBP molecule, after a ligand exchange with *t*-BuOH occurs (**I** → **J**). Detailed energy profile and optimized geometries of intermediates and transition states are given in the Supporting Information.

Although the experimental selectivity is reproduced in the Cu(II) mechanism, the calculated barriers are considerably higher than those found for the Cu(III) 4CRE and CMD-RE mechanisms discussed above, which makes this possibility less likely.

4. CONCLUSIONS

In conclusion, the mechanism of the copper-catalyzed oxidative C−H bond amidation of *N*-methylindole was extensively investigated by means of DFT calculations. The mechanism proposed originally was found to be unable to reproduce the regioselectivity observed experimentally. An unprecedented four-center reductive elimination mechanism, which could account for the observed selectivity, is proposed instead, and the origin of the selectivity was found to be the inherent higher nucleophilicity of C3 of indole as compared to C2. An alternative mechanism involving a Cu(II) intermediate was also investigated and was found to be associated with higher energy barriers. Here it should be noted that, considering the harsh conditions used for this reaction, one cannot exclude that other mechanisms could be operative, possibly with the involvement of radical species. However, with the limited amount of experimental data available, it is difficult to speculate.

Finally, from a technical point of view, we have in this paper shown that the inclusion of an empirical dispersion correction to the B3LYP functional is crucial in order to reproduce the selectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Free energy profile for the amidation through a Cu(I)/Cu(II) mechanism and optimized structures and Cartesian coordinates of all stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) We have also optimized the transition state for this proton transfer step. The energy after all corrections are applied is calculated to be 0.8 kcal/mol higher than **B′** but 0.8 kcal/mol lower than **B″**. Therefore, we consider the endothermicity of the reaction to be the barrier for this step.

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(22) Another possibility to generate Cu(II) is by disproportionation of Cu(I) into Cu(0) and Cu(II). In that case, the initial formation of Cu(III) intermediates is not even necessary. See: Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*; John Wiley & Sons: Hoboken, NJ, 1999.